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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

1059 7590 12/19/2002

BERESKIN AND PARR
SCOTIA PLAZA
40 KING STREET WEST-SUITE 4000 BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/19/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/402,488	MOLONEY ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 November 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): *see attached*.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *NONE*.

   Claim(s) objected to: *NONE*.

   Claim(s) rejected: *1,4-20,23-30 and 41-44*.

   Claim(s) withdrawn from consideration: *31-40 and 45-47*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Note the attached Notice of References Cited (PTO892)*

David J. Steadman
Patent Examiner
Art Unit 1652

ADVISORY ACTION

Status of the Application

1. Claims 1, 4-20, and 23-47 are pending in the application.

2. Claims 31-40 and 45-47 are withdrawn from consideration.

3. Claims 1, 4-20, 23-30, and 41-44 stand finally rejected.

4. Applicants' amendment to claims 1, 4, 6, 13, 20, 23, 25, 41, 42, and 44 and cancellation of claims 2, 3, 21, and 22 in Paper No. 21, filed 11/22/02, is acknowledged and has been entered.

5. The request for reconsideration has been considered but does not place the claims in condition for allowance for the reasons discussed below.

6. The rejection of claims 1, 4, 23, 41, and 42 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "derived from" is withdrawn. Applicants have amended the claims to remove the term "derived from" from the rejected claims, thus obviating the rejection. Claims 2, 3, 21, and 22 have been cancelled, thus obviating the rejection.

7. The scope of enablement rejection of claims 1, 4-20, 23-26, 28-30, and 41-44 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons described below. The rejection was fully explained in previous Office actions (see Paper Nos. 15, 18, and 20). Applicants argue the claims have been amended to narrow the scope of pro-peptides from autocatalytically maturing zymogens to those pro-peptides from autocatalytically maturing aspartic proteases. Applicants argue the specification provides sufficient and clear guidance as to how to use the entire scope of recited aspartic proteases in the methods and compositions of the invention. Applicants argue that in view of the guidance provided in the specification and the comparability of the catalytic mechanism of aspartic proteases, undue experimentation would not be required to make and practice the claimed invention. Applicants' argument is not found persuasive. Undue experimentation would be required for a skilled artisan to make and use the invention as broadly claimed. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). As written, the claims are so broad as to encompass a method of preparing a recombinant polypeptide using a chimeric nucleic acid sequence comprising a nucleic acid encoding *any* pro-peptide from *any* autocatalytically maturing aspartic protease and adding a mature form of *any* autocatalytically maturing zymogen to the resulting fusion protein for cleavage and optionally altering the pH, salt, or temperature conditions or a chimeric nucleic acid encoding a pro-peptide from an autocatalytically maturing aspartic protease and a nucleic acid encoding a heterologous polypeptide. Applicants have provided *only* two working examples of the claimed chimeric nucleic acid sequence, i.e., an expression vector encoding a GST—chymosin pro-peptide—hirudin polypeptide cleavable by treatment with chymosin at pH 4.5 (pages 14 and 15) or a His tag—chymosin pro-peptide—carp growth hormone polypeptide cleavable by treatment with chymosin at pH 2 (page 17, top) or red turnip beetle gut extract (page 17 bottom). It is noted that the two working examples provide only chymosin as the representative autocatalytically maturing aspartic protease. Furthermore, it is noted that only a single representative example of a mature form of an autocatalytically maturing zymogen, i.e, chymosin, was added for cleavage of the fusion protein. While it is noted that Example 3 employs red beetle gut extract for fusion protein cleavage, it is noted that the specification provides no indication as to which autocatalytically maturing zymogen is present in the gut extract. Neither the specification nor the prior art provides sufficient guidance as to which combination of mature forms of autocatalytically maturing zymogens and pro-peptides of aspartic proteases would result in cleavage of a fusion protein from a recombinant protein under any conditions. The specification does not provide guidance as to the altered conditions of pH, salt, or temperature under which cleavage using a particular combination is likely to occur and the prior art (see for example Giam et al. *J Biol Chem* 263:14617-14620) indicates that autoproteolytic activity of HIV acid protease is inhibited in the presence of alkaline buffers (page 14620). Furthermore, it is unclear from the specification and the prior art as to whether any pro-peptide from an autocatalytically maturing aspartic protease will undergo self-cleavage from a heterologous polypeptide

and the specification has not provided the necessary guidance regarding the conditions under which this may occur. Thus, one of skill in the art would recognize the importance of the necessary conditions under which proteolytic cleavage may occur. The specification has provided only a single working example of a pro-peptide/mature protease combination for successful application of the claimed invention, i.e., a chymosin pro-peptide and a mature chymosin. While applicants have provided two examples of heterologous proteases that cleave the chymosin pro-peptide, i.e., Sigma 2143 and Aspergillus saitoi acid protease (see Paper No. 17), the claims are not so limited to a chimeric nucleic acid comprising a nucleic acid encoding only a chymosin pro-peptide and furthermore, it is unpredictable as to whether these proteases (Sigma 2143 and Aspergillus saitoi acid protease) will cleave *any* pro-peptide of *any* aspartic protease. Neither the specification nor the prior art provide sufficient guidance as to which combination of proteases and cleavable heterologous pro-peptides and optionally altered conditions as encompassed by the claims that would obtain the desired biological effect. The expectation of making and using the claimed polynucleotide, host cell, or composition or practicing the claimed method is highly unpredictable and would require an undue amount of experimentation. Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

8. The rejection of claims 1, 4-7, 9-13, 15-20, 23-26, 28-30, and 41-44 under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Moloney (WO 96/21029) is withdrawn. It is noted that applicants' argument addressing the orientation of the nucleic acid as taught by Moloney is not found persuasive. Moloney teaches that a nucleic acid encoding a protease recognition motif can be upstream of a nucleic acid encoding a heterologous polypeptide, i.e., an oil body protein (see Figure 1 and description provided therefor at pages 9 and 10). Furthermore, while Moloney teaches that such a protease recognition motif of Figure 1 (represented by an open circle) can be a chymosin protease recognition site. However, there is no indication in the reference of Moloney that the "protease recognition motif" is intended to be interpreted as a chymosin pro-peptide and one of ordinary skill in the

art, based on the teachings of Moloney, would not necessarily have interpreted the term "protease recognition motif" as used by Moloney to mean a chymosin pro-peptide. Thus, the examiner has determined that Moloney does not teach all limitations of the rejected claims and therefore, the rejection is withdrawn.

9. The rejection of claim 8 under 35 U.S.C. 103(a) as being unpatentable over Moloney in view of McCaman et al. (J Biol Chem 261:15345-15348) is withdrawn. As stated above, there is no indication in the reference of Moloney that the protease recognition motif is intended to be interpreted as a chymosin pro-peptide and one of ordinary skill in the art, based on the teachings of Moloney, would not necessarily have interpreted the term "protease recognition motif" as used by Moloney to mean a chymosin pro-peptide. Therefore, the cited references do not teach all limitations of claim 8 and therefore, the rejection is withdrawn.

10. The rejection of claim 27 under 35 U.S.C. 103(a) as being unpatentable over Moloney in view of Fine et al. (Gen Comp Endocrinol 89:51-61) is withdrawn. As stated above, there is no indication in the reference of Moloney that the protease recognition motif is intended to be interpreted as a chymosin pro-peptide and one of ordinary skill in the art, based on the teachings of Moloney, would not necessarily have interpreted the term "protease recognition motif" as used by Moloney to mean a chymosin pro-peptide. Therefore, the cited references do not teach all limitations of claim 27 and therefore, the rejection is withdrawn.

11. The examiner requests that applicants provide a copy of all pending claims in the response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

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PRIMARY EXAMINER
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